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H1-antihistamines for the treatment of anaphylaxis with and without shock (Review)

Sheikh A, ten Broek VM, Brown SGA, Simons FER

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TABLE OF CONTENTS

[Intervention Review]

H1-antihistamines for the treatment of anaphylaxis with and without shock

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ABSTRACT

Background

Anaphylaxis is an acute systemic allergic reaction, which can be life-threatening. H1-antihistamines are commonly used as an adjuvant therapy in the treatment of anaphylaxis.

Objectives

To assess the benefits and harm of H1-antihistamines in the treatment of anaphylaxis.

Search methods

In our previous version we searched until June 2006. In this version we searched the Cochrane Central Register of Controlled Trials (CENTRAL), (*The Cochrane Library* 2010, Issue 11), MEDLINE (1966 to November 2010); EMBASE (1966 to November 2010); CINAHL (1982 to Nobember 2010) and ISI Web of Science (1945 to November 2010). We also contacted pharmaceutical companies and international experts in anaphylaxis in an attempt to locate unpublished material.

Selection criteria

We planned to include randomized and quasi-randomized controlled trials comparing H1-antihistamines with placebo or no intervention.

Data collection and analysis

Two authors independently assessed articles for inclusion.

Main results

We found no studies that satisfied the inclusion criteria.

Authors' conclusions

Based on this review, we are unable to make any recommendations for clinical practice. Randomized controlled trials are needed, although these are likely to prove challenging to design and execute.

PLAIN LANGUAGE SUMMARY

H1-antihistamines for the emergency treatment of anaphylaxis

Anaphylaxis is a rare, but potentially life-threatening emergency. Evidence from the United Kingdom suggests that incidence may be increasing rapidly. Common triggers of anaphylaxis include a variety of foods, drugs and insect venoms.

H1-antihistamines are commonly used for the emergency treatment of anaphylaxis although the evidence underpinning this treatment is unclear. We therefore conducted a systematic review of the literature searching key databases for high quality published and unpublished material on this subject; in addition, we contacted experts in this area and relevant pharmaceutical companies.

Our searches failed to retrieve any randomized controlled trials on this subject. We conclude there is no evidence from randomized controlled trials to support the use of H1-antihistamines in the emergency management of anaphylaxis.

BACKGROUND

Anaphylaxis is described as a potentially life-threatening, acute systemic allergic reaction with many possible trigger factors, including foods, insect venoms, medications, anaesthetics, latex rubber and exercise (Brown 2001; Brown 2004a; Kemp 2002; Lieberman 2003; Sampson 2005; Simons 2002). It now occurs commonly in the community as well as in healthcare facilities (Simons 2002). Progress is being made towards a universally acceptable clinical definition of anaphylaxis as "a serious allergic reaction that is rapid in onset and may cause death" (Sampson 2006). Historically, it has been defined mechanistically as a hypersensitivity reaction involving the release of mediators from mast cells and basophils following allergen interaction with cell-bound immunoglobulin E (IgE) and has been distinguished from anaphylactoid reactions, which involve non-IgE-mediated or even non-immune release of mediators. This mechanistic distinction is seldom used now, as it is recognized that the clinical picture and the treatment of anaphylaxis are similar regardless of trigger factor or pathophysiologic mechanisms (Kemp 2002; Lieberman 2003).

Anaphylaxis is not a reportable disease and, as such, the true rate of occurrence from all triggers is unknown (Bohlke 2004; Helbing 2004; Klein 1995; Lieberman 2006; Neugut 2001; Peng 2004). Data on the epidemiology of anaphylaxis in the general population are sparse and are influenced by definitions used, coding issues, and misclassification errors. A population-based study of anaphylaxis using data collected in the mid-1980s and possibly before the marked increase in prevalence of allergic diseases, calculated an annual occurrence rate of 30/100,000 person years and raised the concern that anaphylaxis is frequently not recognized by patients and physicians (Yocum 1999). In other recent studies of anaphylaxis caused by a variety of triggers, occurring in the community, presenting to an emergency department, or both, occurrence rates ranged from about eight to 11/100,000 person-years to as high as 590 per 100,000 person-years. There are considerable variations in the occurrence rates of anaphylaxis with age. Admissions coded as anaphylaxis peak in infants aged less than one year, with a second peak in the 20 to 60 year age group (Sheikh 2001). Anaphylaxis from the four most common triggers (foods, insect venoms, medications and latex rubber) may affect more than 1% of the general population (Neugut 2001). There are considerable variations in the age-specific aetiology of anaphylaxis (Alves 2001; Brown 2003); foods predominate in children, and medications and insect stings predominate in adults.

Cutaneous symptoms and signs, including generalized urticaria, angioedema, flushing and itching are the most common manifestations of anaphylaxis, occurring in about 90% of individuals, followed by respiratory symptoms in up to 70%, and gastrointestinal symptoms in up to 40%. Hypotension, manifest as dizziness, shock and unconsciousness or both, occurs in only 10 to 30% of individuals with anaphylaxis (Brown 2001; Brown 2004a; Kemp 2002; Lieberman 2003; Simons 2002). Recognition of the wide spectrum of symptoms and signs in anaphylaxis and of the continuum of symptoms and signs has been emphasized (Sampson 2005).

The time course of anaphylaxis is usually rapid. Symptoms and signs often occur within five to 30 minutes of exposure to the trigger factor, although occasionally they do not develop for several hours. Anaphylaxis may be fatal within five to 30 minutes (Pumphrey 2000). Protracted and biphasic (delayed phase) reactions may occur, although the frequency with which such reactions occur is as yet unclear because of methodological concerns surrounding existent studies; those reporting high rates (up to 25%) are from highly selected groups with particularly severe reactions, whereas those reporting low rates (less than 2%) are retrospective, with potential for under-reporting (Brazil 1998; Douglas 1994; Lee 2000; Sampson 1992; Smit 2005; Stark 1986). Clinically, it may be difficult to distinguish true biphasic (recurrent) reactions from protracted severe reactions where an apparent recurrence in fact represents unmasking of an ongoing reaction when prior adrenaline treatment has worn off.

The diagnosis of anaphylaxis is based largely on history and physical findings at the time of the event. Laboratory tests available to support the diagnosis have proved to be somewhat disappointing in clinical practice. Transiently elevated plasma histamine levels of greater than 10nmol/L correlate with the severity and persistence of cardiopulmonary manifestations or gastrointestinal manifestations. However, as histamine needs to be measured within one hour of the onset of an anaphylaxis episode, and is not stable during routine handling (Lin 2000), this test is seldom used. Identification of an elevated serum tryptase level (greater than 15ng/mL) within 12 hours (preferably within 1 to 3 hours) of the onset of an episode is more widely used as a confirmatory test. The assay for total serum tryptase available in hospital laboratories measures the alpha-tryptase that is constitutively secreted from mast cells, as well as the mature tryptase that is released after mast cell activation in anaphylaxis, and therefore, total serum tryptase levels are often within normal limits in patients with clinically confirmed anaphylaxis (Lee 2000). Serial total serum tryptase measurements may be more helpful than single measurements (Brown 2004b).

Anaphylaxis is under-recognized and under-diagnosed, both in those who survive and those who die. Half of all of those who do not survive an episode of anaphylaxis have no indicative findings at autopsy (Pumphrey 2000). Individuals aged greater than 30 years are more likely to experience hypotensive anaphylaxis, (Brown 2003) and are thus at greatest risk of death from insect sting anaphylaxis, with cardiovascular collapse usually a prominent feature (Pumphrey 2000). In comparison, people who die from food-induced anaphylaxis tend be younger, exhibiting a predominantly respiratory (bronchospastic) reaction pattern, and poorly controlled asthma appears to be a major risk factor for death (Bock 2001; Pumphrey 2000; Sampson 1992).

Adrenaline (epinephrine) is the initial treatment of choice for anaphylaxis. The patient's airway, breathing and circulation need to be assessed, monitored, and managed. In addition to adrenaline, oxygen and inhaled beta-2 agonists are used in the case of breathing difficulties and volume expanders are used in the case of hypotension (Simons 2004a; Walker 2003). As adjuvant therapies H1- and H2-antihistamines and steroids are also often given, although there is little data to support these uses and in the case of first-generation, potentially sedating H1-antihistamine preparations, there is potential to cause harm (Brown 2006; Simons 2004b).

During anaphylaxis, a number of inflammatory mediators are released from mast cells and basophils. Histamine plays a pivotal role in acute allergic inflammation, which is a complex network of events that involve redundant mediators and

signals, including tryptase, carboxypeptidase, platelet-activating factor, prostaglandins, leukotrienes, and cytokines. In a systemic response, however, there may be sufficient redundancy and amplification such that reactions do not respond to a single mediator antagonist (Simons 2004b; Winbery 2002).

In an attempt to down-regulate the allergic response and minimize the clinical impact of histamine release, H1-antihistamines are often given. These medications act as inverse agonists, i.e. they combine with and stabilize the inactive form of the H1-receptor, shifting the equilibrium toward the inactive state (Simons 2004b). There are two main functional classes of H1-antihistamines: first-generation antihistamines, which are sedating, and second-generation antihistamines, which are relatively non-sedating.

OBJECTIVES

To assess the benefits and harm of H1-antihistamines in the treatment of anaphylaxis.

METHODS

Criteria for considering studies for this review

Types of studies

We planned to include randomized controlled trials and quasi-randomized controlled trials comparing H1-antihistamines with placebo or no intervention.

Types of participants

We were interested in all patients (infants, children and adults; community, hospital/medical setting) experiencing anaphylaxis caused by food, insect venom, medication, anaesthetics, latex, exercise, or any other trigger.

Types of interventions

We were interested in studies involving any systemic (intravenous, intramuscular or oral) administration of H1-antihistamines by patient/lay caregiver (of a child) or medical professional.

We intended to examine the use of H1-antihistamines when administered for the treatment of acute anaphylaxis. We specifically excluded any studies where the primary aim was to examine the use of H1-antihistamines for the prevention of anaphylaxis, where the drug under study was not an H1-antihistamine or where the purpose of administration was to prevent rebound or recurrence of anaphylaxis. We intend to examine the use of prophylactic H1-antihistamines in a separate review.

Types of outcome measures

Primary outcomes

The primary outcome measures of interest were:

1. clinical improvement by any objective measure;
2. mortality rate.

Secondary outcomes

We also wished to include data on the following secondary outcome measures:

1. hospitalization rate;
2. length of emergency department visit;
3. length of hospital stay;
4. re-presentation rate to hospital;
5. iatrogenic adverse events;
6. rate of persistent/delayed/biphasic reactions.

Search methods for identification of studies

We searched the Cochrane Central Register of Controlled Trials (CENTRAL, *The Cochrane Library,* 2010 Issue 11 Appendix 1); MEDLINE (Ovid SP, 1966 to November 2010 Appendix 2);EMBASE (Ovid SP, 1966 to November 2010, Appendix 3); CINAHL (EBSCO host, 1982 to November 2010, Appendix 4); and ISI Web of Science (1945 to November 2010 Appendix 5).

We imposed no language restrictions in the literature search.

We searched MEDLINE, using Ovid and the Cochrane randomized controlled trial filter (Higgins 2008) and the following key words: anaphylaxis and H1-antihistamines.

We attempted to uncover additional relevant published data, grey literature, unpublished data and research in progress by:
1. developing a database of first and last authors of potentially eligible studies. We searched The Science Citation Index Expanded (SCI-EXPANDED, 1945 to June 2006) using these names for additional studies;
2. searching the bibliographies of identified studies;
3. compiling a database of international experts in anaphylaxis (see Appendix 6);
4. contacting relevant pharmaceutical companies (see Appendix 6);
5. searching the UK's National Research Register;
6. searching websites listing ongoing trials (http://clinicaltrials.gov/) and (http://www.controlledtrials.com/).

Data collection and analysis

Selection of trials

Two authors (VB, AS) independently reviewed titles and abstracts from literature searches and selected possibly relevant studies. These studies were reviewed in full and assessed using the inclusion criteria detailed above.

We had agreed that we would resolve any disagreements by discussion between both of the authors; in the case of consensus not being reached, a third author (ES) was to be involved, and if necessary, arbitrate, but this did not prove necessary.

Data extraction

Two authors (VB, AS) planned to independently extract data using a suitably adapted version of the data extraction form developed by the Cochrane Anaesthesia Review Group. We agreed to resolve any disagreements by discussion between both of the authors; in the case of consensus not being reached, a third author (ES) would be involved and, if necessary, arbitrate.

Assessment of methodological quality of included studies

In our previous version we planned to grade each parameter of trial quality as: A - low risk of bias; B - moderate risk of bias; C - high risk of bias. We planned to make an overall assessment for each randomized controlled trial, using the same rating scale.

In this updated version of the review we planned to assess the quality of included RCTs following the Cochrane approach using the methods detailed in Chapter Eight of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2008).

We planned to construct risk of bias tables to support judgements of quality using the Cochrane Risk of Bias tool (Higgins 2008):

- Was the allocation sequence adequately generated?
- Was allocation adequately concealed?
- Was knowledge of the allocated interventions adequately prevented during the study?
- Were incomplete outcome data adequately addressed?
- Are reports of the study free of suggestion of selective outcome reporting?
- Was the study apparently free of other problems that could put it at a risk of bias?

We planned to record the judgement as “yes” indicating that the study met that quality parameter, “no” it did not
or “unclear” indicating that there was insufficient evidence to make a judgement either way.We planned to display the results by creating a 'Risk of bias' graph and a 'Risk of bias' summary figure using RevMan 5.0 software

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We also planned to subject quasi-randomized studies to methodological assessment, in which case, two authors (VB, AS) would independently assess study quality: reviewers would not be masked to study details. We planned to assess the agreement of reviewers on methodological quality assessment; and to resolve disagreements by discussion and, if necessary, with the involvement of a third author (ES).

In the event of future trials becoming available, we plan to document the methodological quality of these trials (both randomized and quasi-randomized) following the Cochrane approach using the methods detailed above.

Data analysis

We proposed to use Review Manager (RevMan 5.0) for data analysis and quantitative data synthesis. For dichotomous data, we planned to calculate individual and pooled statistics as relative risks (RR) with 95% confidence intervals (95% CI). For continuous data, we planned to calculate individual and pooled statistics as mean differences (MD) and/or standardized means differences with 95% CI. We planned to consider the appropriateness of meta-analysis in the presence of significant clinical or statistical heterogeneity. We planned to test for heterogeneity using the I^2 statistic. We assumed significant heterogeneity if I^2 was greater than 40% (i.e. more than 40% of the variability in outcome between trials could not be explained by sampling variation) (Higgins 2002). We planned to undertake meta-analysis using fixed effects or random effects modelling, depending on whether or not data are found to be homogenous. In the absence of any statistical or clinical heterogeneity, we planned to report a fixed-model derived pooled effect. We planned to conduct, wherever possible, quantitative analyses of outcomes on an intention-to-treat basis. We planned to assess for evidence of publication bias graphically using Funnel plots and statistically using Begg and Egger tests (Begg 1994; Egger 1997).

Subgroup analysis and investigation of heterogeneity

Where there is evidence of statistical or clinical heterogeneity, we planned to consider undertaking subgroup analysis. Our subgroups of interest are:

1. presence/absence of shock;
2. mild/more severe anaphylaxis (Brown 2004a);
3. class of H1-antihistamine given (sedating/non-sedating and also traditional classification based on chemical structure i.e. ethylenediamine, ethanolamine, alkylamine, phenothiazine, piperazine, piperidine and other);
4. mode of administration of treatment (for example, intravenous versus intramuscular versus oral);
5. time from onset of anaphylaxis to receiving treatment;
6. age (infant, child, adult).

Sensitivity analysis

We planned to undertake sensitivity analysis for the allocation of missing data by best and worst-case analysis and also to undertake sensitivity analysis on the basis of only including randomized studies. This would allow an assessment of the impact on the review conclusions of excluding studies judged to be at high risk of bias.

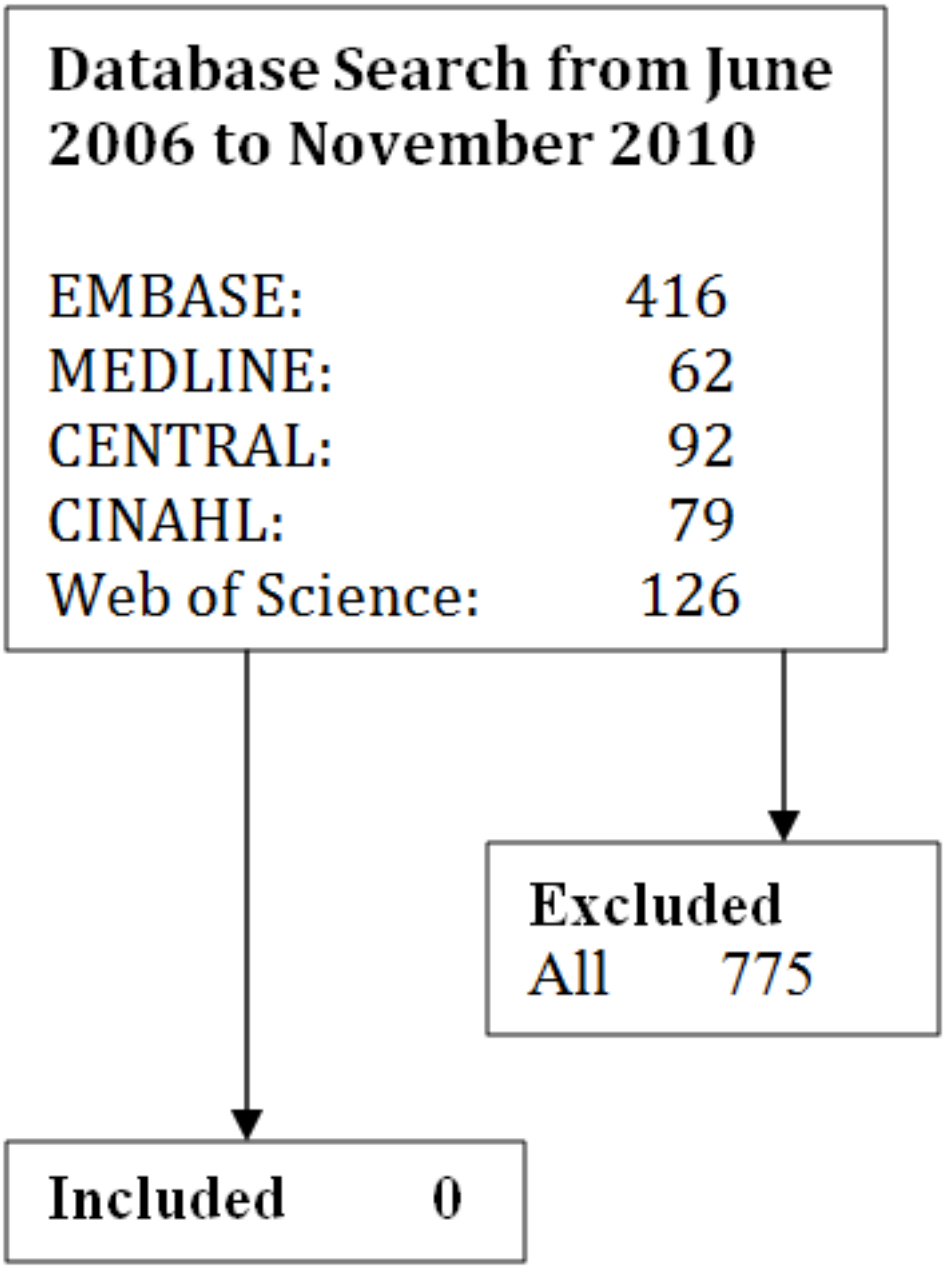
RESULTS

Description of studies

In the previous version we searched the Searching the four databases until June 2006 and this yielded 2070 citations. After scrutiny of the abstracts of these studies, only one article (Runge 1992) was retrieved for full text analysis, but this did not fulfil the inclusion criteria on account of the allergic reactions being studied and the absence of a suitable control group (see table 'Characteristics of excluded studies'). The search of the UK National Research Register, Current Controlled Trials and ClinicalTrials.gov using anaphylaxis as a keyword identified no useful articles. We contacted context editors and pharmaceutical companies (Appendix 6) but this did not contribute any published or unpublished studies.

In this updated version we searched the databases from June 2006 to November 2010 and found an additional 775 citations (2845 citations in total). After scrutiny of these 775 citations none fulfilled our inclusion criteria (see Figure 1).

Figure 1. Search flow diagram



Risk of bias in included studies

There were no eligible studies (see table 'Characteristics of excluded studies').

Effects of interventions

There were no eligible studies (see table 'Characteristics of excluded studies').

DISCUSSION

We have found no high quality evidence either for or against the use of H1-antihistamines in anaphylaxis.

Anaphylaxis is an emergency situation. To help ensure appropriate standards of care, guidelines have been developed in several countries. For example, the guideline on anaphylaxis used in the UK advises that, after oxygen and adrenaline (epinephrine) are given, patients should receive an H1-antihistamine and, if needed, additional treatments with fluids or hydrocortisone (Resusicitation 2005). H1-antihistamines are seen to have a role in the treatment of anaphylaxis in this and many other guidelines, although the evidence base in support of this position remains very weak.

H1-antihistamines are effective in some localized and less severe systemic allergic reactions; for example in allergic rhinitis they relieve sneezing, itching, and rhinorrhea; in allergic conjunctivitis

they relieve erythema, itching, and lacrimation; and in urticaria they relieve itching and whealing, as documented in systematic literature reviews (Owen 2004; Vanden Bussche 1987). In other allergic disorders, they are of little clinical importance. The evidence-based UK guideline on asthma, for example, does not recommend treatment with H1-antihistamines (SIGN/BTS 2005). Furthermore, a systematic literature review conducted on atopic dermatitis could not demonstrate a beneficial effect of H1-antihistamines (Klein 1999). Generalisations to anaphylaxis based on their effectiveness (or ineffectiveness) in other allergic disorders are therefore problematic.

Although H1-antihistamines are expected to relieve itching, hives, other cutaneous symptoms, and rhinorrhea in anaphylaxis, they are not expected to relieve airway obstruction, gastrointestinal symptoms, or shock, nor do they prevent ongoing mediator release from mast cells and basophils in doses used clinically (Simons 2004a). Moreover, after administration by mouth, H1-antihistamine absorption and onset of action are slow, taking at least one to two hours (Simons 2004a). Most medications in this large class cannot be administered by injection, with the exception of a few first-generation H1-antihistamines such as chlorpheniramine, diphenhydramine, hydroxyzine and pomethazine (Simons 2004a). In many episodes of anaphylaxis, improvement attributed to an orally administered H1-antihistamine is likely to be due to spontaneous improvement or endogenous compensatory mechanisms such as increased epinephrine and angiotensin II secretion (van der Linden 1993; Simons 2006).

It is also important to bear in mind that treatment with H1-antihistamines may have side effects. The first-generation H1-antihistamines cross the blood-brain barrier and in usual doses may cause drowsiness, fatigue, somnolence, dizziness, confusion, impairment of cognitive function, and other CNS symptoms. In infants and young children, paradoxical CNS stimulation, including seizures, can occur. Hypotension and dose-related cardiac toxic events have been reported (Simons 2004b). Overdose of first-generation H1-antihistamines has led to fatalities. In contrast, second-generation H1-antihistamines are relatively non-toxic (Hindmarch 2001; Winbery 2002; Simons 2004b); however, they are not available for parenteral use.

As the evidence suggests that H1-antihistamines are effective only in some less severe allergic disorders; that administration of H1-antihistamines may cause important side-effects, and that the existing studies investigating their role in anaphylaxis have used sub-optimal study-designs. One may then, reasonably ask why there are as yet no randomized controlled trials (RCTs) in this area? We hypothesize that one of the primary reasons there are no RCTs might be the fact that anaphylaxis represents a potentially life-threatening emergency. Executing a RCT in an emergency situation raises a number of ethical questions. For example, how can informed consent be obtained? How can one refuse a possible treatment option in an emergency? How can one get approval for the use of a placebo?

We consider these important considerations below:

How should informed consent be obtained?
Paragraph 26 of the Declaration of Helsinki states that: "in an emergency context, consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate" (WMA 2004). No direct consent is needed, which makes it, in principle, ethically feasible to conduct a randomized controlled trial in this context; however, the Declaration of Helsinki has no legal effect. The European Union agreements do, however, have legal weight (Lotjonen 2002). Within these agreements, the patient or his/her legal representative should be informed about the purposes and risks of the trial, before entering it. To inform someone and to find a legal representative takes time; time which typically is not available in an emergency situation (Directive 2001/20/EC). Currently, an amendment has been proposed by the UK in which an exception for emergency situations has been proposed. This exception implies that before entering a trial no direct informed consent is needed. Consent must be given within 24 hours (MLX 326 2004). Approval of this amendment will facilitate the execution of randomized controlled trials in emergency situations.

How can one refuse a possible treatment option in an emergency?
H1-antihistamines are seen as a possible treatment option because a number of guidelines recommend their use. This recommendation has been incorporated into guidelines without a proven effect ever being demonstrated. There might be no effect, or the side effects might be worse than the effect itself. It can therefore be argued that there is a state of clinical equipoise between H1-antihistamines and placebo. However, to examine this in the presence of current guidelines may prove difficult.

How can approval for the use of a placebo be obtained?
The argument mentioned above can also be used here. When a state of clinical equipoise exists, a comparison between antihistamine treatment and placebo should be possible. Although rare, there are placebo-controlled trials done in emergency situations. Two that are of possible relevance will be described here. The first study (Habib 1995) was a prospective, randomized, double-blind, placebo-controlled clinical trial, designed to evaluate the safety and efficacy of oral nicardipine for the treatment of urgent hypertension in the emergency department. The control group was treated with a placebo. Individuals who didn't respond to their first treatment got a second tablet of open-label nicardipine. The study however excluded the hypertensive emergencies. Another study (Alldredge 2001) examined the administration of benzodiazepines by paramedics for out-of-hospital status epilepticus. Patients were given intravenous diazepam, lorazepam, or placebo. Two treatments: waiting or giving benzodiazepines were compared. An open-label diazepam was immediately available when the patient was at high risk for a life-threatening complication. While these randomized controlled trials are not directly comparable to investigation of H1-antihistamines in anaphylaxis, their existence may provide useful information relevant to the design of a future randomized controlled trials of H1-antihistamine treatment in anaphylaxis.

The second reason for the absence of randomized controlled trials in anaphylaxis could be linked with the absence of a universally-accepted definition on this topic. Many emergency departments work with their own definitions and this hinders standardized research and treatment (Clark 2004). This issue has been repeatedly highlighted (Brown 2004a; Sampson 2005; Sampson 2006).

A third reason for their absence might be the perceived relevance of our research question. Why should we want to know what the effects are of H1-antihistamine treatment in anaphylaxis? This might not be the most important question asked. But given that anaphylaxis is a life-threatening disease with potentially

avoidable mortality, we have no hesitation in arguing for the need for robust data to guide clinical decision-making. Moreover, the administration of H1-antihistamines potentially delays the use of other, perhaps more effective, treatment modalities.

Finally, designing trials for conditions with a low incidence/prevalence and interventions with likely modest effect sizes is challenging, as the studies need to be large in order to have adequate power. The number of patients required may thus be prohibitive.

Considering the above points, there are many challenges inherent in conducting a controlled trial in this area. These challenges need to be weighed up against the possible advantages of generating robust evidence. Given the lack of findings uncovered by this comprehensive review, we believe, the ethics and feasibility of mounting and successfully executing a randomized controlled trial of H1-antihistamines now warrants broader discussion and debate.

AUTHORS' CONCLUSIONS

Implications for practice

We found no relevant evidence. We are therefore unable to make recommendations about H1-antihistamine use in the treatment of anaphylaxis. Guidelines on the management of anaphylaxis need to be much more explicit about the basis of their recommendations regarding the use of H1-antihistamines.

Implications for research

Given the routine use of H1-antihistamines in some centres, there is a case for randomized trials of high methodological rigour in order to define the true extent of benefit from the administration of H1-antihistamines in anaphylaxis. Specifically, more information is required on the subset of patients most likely to benefit from this therapy and the most appropriate preparations, route and dose of administration. Any future trials would need to consider in particular:

- appropriate sample sizes with power to detect expected differences
- careful definition and selection of target patients
- appropriate comparator therapy
- appropriate outcome measures including all those listed in this review
- careful elucidation of any adverse effects and
- the cost-utility of the therapy.

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CHARACTERISTICS OF STUDIES

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Runge 1992	Not studying patients with anaphylaxis. No control group

APPENDICES

Appendix 1. Search strategy for CENTRAL, *The Cochrane Library*

#1 MeSH descriptor Anaphylaxis explode all trees
#2 anaphyla*
#3 anaphyla* near (shock* or syndrome* or react*)
#4 anaphyla* and (shock* or syndrome* or react*)
#5 acute systemic allergic react*
#6 idiopathic anaphylaxis
#7 systemic anaphylaxis
#8 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7)
#9 MeSH descriptor Histamine H1 Antagonists explode all trees
#10 antihistamin*
#11 Benadryl or Livostin direct or opatanol or emadine or relestat or optilast or nytol or dreemon or medinex or nightcalm or panadolnight or clarityn allergy or nyquil or sinequan or xepin or pbz-sr or tacaryl or hismanal or kestine or ebastel or clistin or dramamine or tussirex

or antivert or tinset ped or optimine or stugeron or stugeron forte or sibelium or histadyl or polaramine or alomide or rizaben or zyrtec or claritin or coricidin or soltara or allegra or alavert or tavist or Chlorpheniramin* or brompheniramin* or Dimethinden* or Pheniramin* or Triprolidin* or Buclizin* or Cyclizin* or Hydroxyzin* or Meclizin* or Oxatomid* or Azatadin* or Cyproheptadin* or Diphenylpyralin* or Ketotifen or Carbinoxamin* or Clemastin* or Dimenhydrinat* or Diphenhydramin* or Doxylamin* or Phenyltoloxamin* or Antazolin* or Pyrilamin* or Tripelennamin* or Methdilazin* or Promethazin* or Doxepin or Alimemazine Tartrate or Acrivastin* or Cetirizin* or Levocetirizin* or Astemizol* or Desloratadin* or Ebastin* or Fexofenadin* or Levocabastin* or Loratadine or loratidine or Mizolastin* or Olopatadin* or Terfenadin* or Azelastin* or Emedastin* or Epinastin* or Cinnarizin* or Flunarizin* or Methapyrilen* or Mianserin or Actifed or carebastin* or chloropyramin* or dexchlorpheniramin* or lodoxamide tromethamine or mequitazin* or mirtazapin* or NCO 650 or picumast or protopin* or proxicromil or temelastin* or Tranilast* or tritoqualin* or Valoid or Otrivine or Antistin or Zaditen or Phenergan or Atarax or Ucerax or Tavegil or Periactin or Piriton or Dimotane or Vallergan or Mizollen or Xyzal or Telfast or Neoclarityn
#12 (#9 OR #10 OR #11)
#13 (#8 AND #12)

Appendix 2. Search strategy for MEDLINE (Ovid SP)

1. (Anaphylact$ or anaphylax$ or idiopathic is or (acute adj5 allergic react$)).mp. or exp ANAPHYLAXIS/
2. MIANSERIN/ or METHAPYRILENE/ or FLUNARIZINE/ or CINNARIZINE/ or TERFENADINE/ or LORATADINE/ or ASTEMIZOLE/ or CETIRIZINE/ or DOXEPIN/ or PROMETHAZINE/ or TRIPELENNAMINE/ or PYRILAMINE/ or ANTAZOLINE/ or DOXYLAMINE/ or DIPHENHYDRAMINE/ or DIMENHYDRINATE/ or CLEMASTINE/ or KETOTIFEN/ or CYPROHEPTADINE/ or MECLIZINE/ or HYDROXYZINE/ or CYCLIZINE/ or TRIPROLIDINE/ or PHENIRAMINE/ or DIMETHINDENE/ or BROMPHENIRAMINE/ or CHLORPHENIRAMINE/ or exp Histamine H1 Antagonists/ or (Neoclarityn or Telfast or Xyzal or Mizollen or Vallergan or Dimotane or Piriton or Periactin or Periactin or Tavegil or Ucerax or Atarax or Phenergan or Zaditen or Otrivine-Antistin or Valoid or tritoqualine or Tranilast or temelastine or proxicromil or protopine or picumast or NCO 650 or mirtazapine or mequitazine or lodoxamide tromethamine or dexchlorpheniramine or chloropyramine or carebastine or Actifed or Mianserin or Methapyrilene or Flunarizine or Cinnarizine or Epinastine or Emedastine or Azelastine or Terfenadine or Olopatadine or Mizolastine or Loratadine or Levocabastine or Fexofenadine or Ebastine or Desloratadine or Astemizole or Levocetirizine or Cetirizine or Acrivastine or Alimemazine Tartrate or Doxepin or Promethazine or Methdilazine or Tripelennamine or Pyrilamine or Antazoline or Phenyltoloxamine or Doxylamine or Diphenhydramine or Dimenhydrinate or Clemastine or Carbinoxamine or Ketotifen or Diphenylpyraline or Cyproheptadine or Azatadine or Oxatomide or Meclizine or Hydroxyzine or Cyclizine or Buclizine or Triprolidine or Pheniramine or Dimethindene or brompheniramine or Chlorpheniramine or antihistamin$ or Benadryl or Livostin direct or opatanol or emadine or relestat or optilast or nytol or dreemon or medinex or nightcalm or panadolnight or clarityn allergy or nyquil or sinequan or xepin or pbz-sr or tacaryl or hismanal or kestine or ebastel or clistin or dramamine or tussirex or antivert or tinset ped or optimine or stugeron or stugeron forte or sibelium or histadyl or polaramine or alomide or rizaben).mp.
3. 1 and 2
4. ((randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or placebo.ab. or clinical trials as topic.sh. or randomly.ab. or trial.ti.) not (animals not (humans and animals)).sh.
5. 3 and 4

Appendix 3. Search strategy for EMBASE (Ovid SP)

1. (Anaphylact$ or anaphylax$ or idiopathic is or (acute adj5 allergic react$)).mp. or exp ANAPHYLAXIS/ or exp ANAPHYLACTIC SHOCK/
2. MIANSERIN/ or METHAPYRILENE/ or FLUNARIZINE/ or CINNARIZINE/ or TERFENADINE/ or LORATADINE/ or ASTEMIZOLE/ or CETIRIZINE/ or DOXEPIN/ or PROMETHAZINE/ or TRIPELENNAMINE/ or mepyramine/ or ANTAZOLINE/ or DOXYLAMINE/ or DIPHENHYDRAMINE/ or DIMENHYDRINATE/ or CLEMASTINE/ or KETOTIFEN/ or CYPROHEPTADINE/ or meclozine/ or HYDROXYZINE/ or CYCLIZINE/ or TRIPROLIDINE/ or PHENIRAMINE/ or dimetindene/ or BROMPHENIRAMINE/ or CHLORPHENIRAMINE/ or exp Histamine H1 Antagonists/ or (Neoclarityn or Telfast or Xyzal or Mizollen or Vallergan or Dimotane or Piriton or Periactin or Periactin or Tavegil or Ucerax or Atarax or Phenergan or Zaditen or Otrivine-Antistin or Valoid or tritoqualine or Tranilast or temelastine or proxicromil or protopine or picumast or NCO 650 or mirtazapine or mequitazine or lodoxamide tromethamine or dexchlorpheniramine or chloropyramine or carebastine or Actifed or Mianserin or Methapyrilene or Flunarizine or Cinnarizine or Epinastine or Emedastine or Azelastine or Terfenadine or Olopatadine or Mizolastine or Loratadine or Levocabastine or Fexofenadine or Ebastine or Desloratadine or Astemizole or Levocetirizine or Cetirizine or Acrivastine or Alimemazine Tartrate or Doxepin or Promethazine or Methdilazine or Tripelennamine or Pyrilamine or Antazoline or Phenyltoloxamine or Doxylamine or Diphenhydramine or Dimenhydrinate or Clemastine or Carbinoxamine or Ketotifen or Diphenylpyraline or Cyproheptadine or Azatadine or Oxatomide or Meclizine or Hydroxyzine or Cyclizine or Buclizine or Triprolidine or Pheniramine or Dimethindene or brompheniramine or Chlorpheniramine or antihistamin$ or Benadryl or Livostin direct or opatanol or emadine or relestat or optilast or nytol or dreemon or medinex or nightcalm or panadolnight or clarityn allergy or nyquil or sinequan or xepin or pbz-sr or tacaryl or hismanal or kestine or ebastel or clistin or dramamine or tussirex or antivert or tinset ped or optimine or stugeron or stugeron forte or sibelium or histadyl or polaramine or alomide or rizaben).mp.
3. 1 and 2
4. (placebo.sh. or controlled study.ab. or random*.ti,ab. or trial*.ti,ab.) not (animals not (humans and animals)).sh.
5. 3 and 4

Appendix 4. Search strategy for CINAHL (EBSCO host)

S1 (MM "Anaphylaxis")

S2 TX Anaphylact* or anaphylax*
S3 AB acute and AB allergic react*
S4 S1 or S2 or S3
S5 (MM "Histamine H1 Antagonists+") OR (MM "Histamine H2 Antagonists+")
S6 TX Neoclarityn or Telfast or Xyzal or Mizollen or Vallergan or Dimotane or Piriton or Periactin or Periactin or Tavegil or Ucerax or Atarax or Phenergan or Zaditen or Otrivine-Antistin or Valoid or tritoqualine or Tranilast or temelastine or proxicromil or protopine or picumast or NCO 650 or mirtazapine or mequitazine or lodoxamide tromethamine or dexchlorpheniramine or chloropyramine or carebastine or Actifed or Mianserin or Methapyrilene or Flunarizine or Cinnarizine or Epinastine or Emedastine or Azelastine or Terfenadine or Olopatadine or Mizolastine or Loratadine or Levocabastine or Fexofenadine or Ebastine or Desloratadine or Astemizole or Levocetirizine or Cetirizine or Acrivastine or Alimemazine Tartrate or Doxepin or Promethazine or Methdilazine or Tripelennamine or Pyrilamine or Antazoline or Phenyltoloxamine or Doxylamine or Diphenhydramine or Dimenhydrinate or Clemastine or Carbinoxamine or Ketotifen or Diphenylpyraline or Cyproheptadine or Azatadine or Oxatomide or Meclizine or Hydroxyzine or Cyclizine or Buclizine or Triprolidine or Pheniramine or Dimethindene or brompheniramine or Chlorpheniramine or antihistamin$ or Benadryl or Livostin direct or opatanol or emadine or relestat or optilast or nytol or dreemon or medinex or nightcalm or panadolnight or clarityn allergy or nyquil or sinequan or xepin or pbz-sr or tacaryl or hismanal or kestine or ebastel or clistin or dramamine or tussirex or antivert or tinset ped or optimine or stugeron or stugeron forte or sibelium or histadyl or polaramine or alomide or rizaben
S7 S5 or S6
S8 S4 and S7

Appendix 5. Search strategy for ISI Web of Science

#1 TS=(Anaphylact* or anaphylax*) or TS=(acute SAME (allergic react*))
#2 TS=(Histamine H1 Antagonists or Neoclarityn or Telfast or Xyzal or Mizollen or Vallergan or Dimotane or Piriton or Periactin or Periactin or Tavegil or Ucerax or Atarax or Phenergan or Zaditen or Otrivine-Antistin or Valoid or tritoqualine or Tranilast or temelastine or proxicromil or protopine or picumast or NCO 650 or mirtazapine or mequitazine or lodoxamide tromethamine or dexchlorpheniramine or chloropyramine or carebastine)
#3 TS=(Actifed or Mianserin or Methapyrilene or Flunarizine or Cinnarizine or Epinastine or Emedastine or Azelastine or Terfenadine or Olopatadine or Mizolastine or Loratadine or Levocabastine or Fexofenadine or Ebastine or Desloratadine or Astemizole or Levocetirizine or Cetirizine or Acrivastine or Alimemazine Tartrate or Doxepin or Promethazine or Methdilazine or Tripelennamine or Pyrilamine or Antazoline or Phenyltoloxamine or Doxylamine)
#4 TS=(Diphenhydramine or Dimenhydrinate or Clemastine or Carbinoxamine or Ketotifen or Diphenylpyraline or Cyproheptadine or Azatadine or Oxatomide or Meclizine or Hydroxyzine or Cyclizine or Buclizine or Triprolidine or Pheniramine or Dimethindene or brompheniramine or Chlorpheniramine or antihistamin* or Benadryl or Livostin direct or opatanol or emadine)
#5 TS=(relestat or optilast or nytol or dreemon or medinex or nightcalm or panadolnight or clarityn allergy or nyquil or sinequan or xepin or pbz-sr or tacaryl or hismanal or kestine or ebastel or clistin or dramamine or tussirex or antivert or tinset ped or optimine or stugeron or stugeron forte or sibelium or histadyl or polaramine or alomide or rizaben)
#6 #5 OR #4 OR #3 OR #2
7#6 AND #1
#8 TS=(random* or placebo or multicenter or prospective) or TS=((controlled or clinical) SAME trial*) or TS=((single or double or triple or treble) SAME (mask* or blind*))
#9 #8 AND #7

Appendix 6. List of experts and pharmaceutical companies contacted

People/companies

Dr. A. Bock;
Prof. A. Brown;
Dr. C.A. Camargo;
Dr. S. Clark;
Dr. P.W. Ewan;
Prof. M. Fisher;
Dr. D. Golden;
Dr. A. Helbling;
Dr. S. Kemp;
Dr. P.L. Lieberman;
Dr. R.Y. Lin;
Dr. R. Lockey;
Prof. D.A. Moneret-Vautrin;
Prof. U. Muller;
Prof. J.M. Negro-Alvarez;
Dr. R.S Pumphrey;
Prof. J. Ring;

Prof. H.A. Sampson

Amdipharm;
Aventis Pharma,
Cambridge Healthcare Supplies;
GlaxoSmithKline Consumer Healthcare;
Novartis Consumer Health;
Rhone-Poulenc Rorer;
Schering-Plough;
Schwarz;
Viatris Pharmaceuticals

WHAT'S NEW

Date	Event	Description
14 December 2018	Amended	Editorial team changed to Cochrane Emergency and Critical Care
18 June 2014	Review declared as stable	This Cochrane review has been marked as 'stable no longer being updated' as there are no randomized controlled trials (RCTs) and for ethical reasons there are unlikely to be any RCTs in the future. If the situation changes, then the authors will update the review.

HISTORY

Protocol first published: Issue 3, 2006
Review first published: Issue 1, 2007

Date	Event	Description
29 January 2016	Amended	The lead author's contact details have been updated.
13 March 2012	Amended	Contact details updated.
18 January 2012	Amended	Contact details updated.
30 November 2010	New search has been performed	In the previous version of our review we ran the database searches until June 2006. In this version we reran the database searches until November 2010. We found no new studies that fitted our inclusion criteria. We updated the methods section.
31 August 2010	Amended	Contact details updated.
17 March 2010	Amended	Aziz Sheikh's affiliation updated
21 June 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

Conceiving the review: ES and AS

Co-ordinating the review: AS
Undertaking manual searches: VB
Screening search results: VB and AS
Organizing retrieval of papers: VB
Screening retrieved papers against inclusion criteria: VB and AS
Appraising quality of papers: VB and AS
Abstracting data from papers: Not applicable
Writing to authors of papers for additional information: VB and AS
Providing additional data about papers: Not applicable
Obtaining and screening data on unpublished studies: Not applicable
Data management for the review: VB
Entering data into Review Manager (RevMan 5.0): VB
RevMan statistical data: Not applicable
Other statistical analysis not using RevMan: Not applicable
Double entry of data: (data entered by person one: ; data entered by person two:) Not applicable
Interpretation of data: Not applicable
Statistical inferences: Not applicable
Writing the review: AS, ES, VB and SB
Securing funding for the review: Not applicable
Performing previous work that was the foundation of the present study: AS, ES and SB
Guarantor for the review (one author): AS
Person responsible for reading and checking review before submission: AS

DECLARATIONS OF INTEREST

None known

INDEX TERMS

Medical Subject Headings (MeSH)

Anaphylaxis [*drug therapy]; Emergency Treatment; Histamine H1 Antagonists [*therapeutic use]; Shock [*complications]

MeSH check words

Humans